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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,268	10/15/2003	Pankaj Agarwal	GP50029-1	9955

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EXAMINER	
BRANNOCK, MICHAEL T	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/687,268	AGARWAL ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/10/05

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) 4-13 and 15-25 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 and 14 is/are rejected.

7)☒ Claim(s) 2 and 3 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 15 October 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 011005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 09/27/2004, have been entered in full.

Applicant's election 5/3/05 with traverse of Group I (original claims 1-3 and 14, 15) the species of SEQ ID NO: 35 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)). The examiner finds that claims 1-3 and 14 read on the elected species.

Claims 4-13 and 15-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/3/05.

Information Disclosure Statement

The information disclosure statement filed January 10, 2005 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the document cited as "Copy of Partial EP Search Report" does not provide enough reference information to lead the reader to the document and therefore not in compliance with 37 CFR 1.98(b)(5). This document has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information

contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Furthermore, a new title of the invention is required' because the word "novel" is not considered as part of the title of an invention and the Patent and Trademark Office does not include such words at the beginning of the title of an invention. It is suggested that the word "novel" be deleted from the title of the invention . See MPEP 606.01.

The disclosure is objected to because of the following informalities: at page 3 line 28 "wound" is misspelled.

Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 29 for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim requires a pharmaceutical composition comprising an effective amount of the polypeptide yet the claims nor the specification specifically assert what amount is to be effective for.

The common phrase "an effective amount" may or may not be indefinite. The proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. See In re Mattison, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The phrase "an effective amount . . . for growth stimulation" was held to be definite where the amount was not critical and those skilled in the art would be able to determine from the written disclosure, including the examples, what an effective amount is. In re Halleck, 422 F.2d 911, 164 USPQ 647 (CCPA 1970). The phrase "an effective amount" has been held to be indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. In re Fredericksen 213 F.2d 547, 102 USPQ 35 (CCPA 1954). The more recent cases have tended to accept a limitation such as "an effective amount" as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim. In Ex parte Skuballa, 12 USPQ2d 1570 (Bd.

Pat. App. & Inter. 1989), the Board held that a pharmaceutical composition claim which recited an "effective amount of a compound of claim 1" without stating the function to be achieved was definite, particularly when read in light of the supporting disclosure which provided guidelines as to the intended utilities and how the uses could be effected.

In the instant case, at page 66-67 the specification provides a myriad of disparate, generalized and ill-defined disease states that the polypeptide may be involved in. Further, the specification provides no information with particular respect to pharmaceutical compositions of SEQ ID NO: 35. Thus, the artisan could not be sure that he was in possession of an amount of SEQ ID NO: 35 that would infringe on Applicant's claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides of SEQ ID NO: 35, and fragments thereof suitable for producing antibodies specific for SEQ ID NO: 2, and fragments thereof with additional heterologous sequences, e.g. epitope tags or carrier proteins, does not reasonably provide enablement polypeptide variants having at least 95% identity to SEQ ID NO: 35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The vast majority of in the claimed genus are polypeptides are amino acid sequence variants of SEQ ID NO: 35, i.e. amino acid substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 35, yet the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, the has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 35 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 35 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 35 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 35. Conversely, if a protein variant of SEQ ID NO: 2 need not have a disclosed property, the specification has failed to teach how to use such a variant.

The wound healing enhancement activity, disclosed on pages 88-90 and figure 1, was presumably accomplished with expression by adenovirus of a polypeptide of SEQ ID NO: 46, which is asserted to be the murine homologue (ortholog) of the human SEQ ID NO: 35 having less than 95% identity with SEQ ID NO: 35. Again, presumably, SEQ ID NO: 35 and 46 would be expected to have similar properties. However, the specification has not provided a working example of the use of a variant of the polypeptide of SEQ ID NO: 35, encompassed by the claims, nor sufficient guidance so as to enable one of skill in the art to make such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 35 could be modified so as to

produce a polypeptide that is not identical to SEQ ID NO: 35 and still retain any activity of the polypeptide of SEQ ID NO: 35.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). Guo-HH et al. PNAS 101(25)9205-9210, 2004, recently reviewed the art and conducted an extensive study on the effect of amino acid substitution on the functionality of a wide variety of proteins and found that on average a single amino acid substitution had a 34% chance inactivating the functionality of the protein, see the Abstract. The specification has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992.

Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 35 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Additionally, claim 14 requires a pharmaceutical composition comprising an effective amount of the polypeptide of SEQ ID NO: 35. No such particular composition is taught in the specification, and it appears that the wound healing activity of the polypeptide requires transgenic expression by a virus (page 90). Thus, one would expect that to be able to use the polypeptide to treat a disorder, as required by the phrase "pharmaceutical composition" considerations other than simply placing the polypeptide in a pharmaceutically acceptable carrier must be required to make the amount effective, e.g. delivery systems, controlled release, carriers,

or stabilizers as broadly reviewed at pages 20-25 of the specification. However no particulars are taught with regard to SEQ ID NO: 35, thus one skilled in the art would expect that the further research and investigation required to make such a composition would be unduly burdensome, if indeed such a composition can be made. In *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claimed composition does not appear to be developed to the point-where specific benefit exists in currently available form.

Due to the large quantity of experimentation necessary to generate the infinite number of variant recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a single polypeptide of SEQ ID NO: 35, yet the claims encompass polypeptides not described in the specification, i.e. polypeptide sequences from other primate species that might be expected to be at least 95% identical to the human sequences, mutated sequences or allelic variants, yet which retain any useful functional limitations. The specification contemplates these variants, e.g. see page 4 and the claims encompass these variants; yet none of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. The skilled artisan would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polypeptide of SEQ ID NO: 35, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, only one naturally

occurring polypeptide sequence, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

With the exception of the polypeptide of SEQ ID NO: 35, the skilled artisan cannot envision the detailed chemical structure of the encompassed variants and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the polypeptide of SEQ ID NO: 35, fragments thereof, and heterologous fusions thereof, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Additionally, claim 14 requires a pharmaceutical composition comprising an effective amount of the polypeptide of SEQ ID NO: 35. No such particular composition is taught in the specification, and it appears that the wound healing activity of the polypeptide requires transgenic expression by a virus (page 90). Thus, one would expect that to be able to use the

polypeptide to treat a disorder, as required by the phrase "pharmaceutical composition" considerations other than simply placing the polypeptide in a pharmaceutically acceptable carrier must be required to make the amount effective, e.g. delivery systems, controlled release, carriers, or stabilizers as broadly reviewed at pages 20-25 of the specification. However no particulars are taught with regard to SEQ ID NO: 35, thus one skilled in the art would not consider Applicant to be in possession of the claimed composition.

Allowable Subject Matter

Claims 2 and 3 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

MB

July 24, 2005